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Denham, Alison, McIntyre, Michael and Whitehouse, Jule Kava - the unfolding story: Report on a work-in-progress. Journal of Alternative and Complementary Medicine, 8 (3). pp. 237-263.

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SPECIAL REPORT

Kava—the Unfolding Story: Report on a Work-in-Progress

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ABSTRACT

This paper, originated as a submission (now updated) to the U.K. Medicines Control Agency and Committee of Safety of Medicines (CSM) on January 11, 2002, in response to a report circulated by the German Federal Institute for Drugs and Medical Products (German initials are BfArM), a compilation of which is summarized in Appendix 2. This agency issued notification in late November 2001 of some thirty adverse events associated with the use of concentrated standardized preparations of kava (*Piper methysticum*, Forst. f.) reported from Germany and Switzerland. An analysis of the summary of the BfArM case reports (see Appendix 2) shows that these contain duplications among the cases cited. The original submission that was sent to the CSM January 2002 has been updated to the version published here. This new version was completed in April 2002.

As a result of the alert from BfArM, the evaluation of kava's safety is now occurring on a worldwide basis and, being that this a matter of considerable importance to the public, the health care community, and regulatory authorities as well as to kava farmers throughout Polynesia, it is important to depict this progress report. As such, this updated report does not provide final answers. The material released by the BfArM is lacking in detail; however, it is hoped that this report will shed light on the kava controversy. It is anticipated that there will be further updates shortly.

This report, prepared on behalf of the Traditional Medicines Evaluation Committee, a subcommittee of the European Herbal Practitioners Association, argues that many of the adverse events cited by the BfArM should not be attributed to kava. In addition, the report states that the properties of concentrated standardized kava extracts—as opposed to preparations that closely approximate those created for traditional use—contribute to causing adverse events. This report proposes a number of simple measures that will ensure that safe kava preparations may continue to be available in the United Kingdom.

BENEFITS OF KAVA

Kava (*Piper methysticum*, Forst. f.) is an important herbal medicine with unique properties. The ability of herbal practitioners to

care for their patients would be significantly affected if this herb's use were restricted or curtailed so that practitioners were unable to prescribe it. Since the early 1900s, kava has been used in Britain by herbal practitioners, mainly

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for urinary problems (Ellingwood, 1919). The indications given in the *British Herbal Pharmacopoeia* (Anonymous, 1983) are "Cystitis, Urethritis, Rheumatism, and Infection of the genito-urinary tract." More recent texts emphasize the herb's usage as a nervine. For example, indications given by Mills and Bone (2000) are "anxiety of nervous origin, nervous tension, restlessness or mild depression of non-psychotic origin, menopausal symptoms and inflammation and infections of the genitourinary tracts of both men and women; muscular and nervous pain; and insomnia." Kava use as a nervine (which is its traditional therapeutic use) has increased markedly in recent years partly because of the evidence for clinical effectiveness found in clinical trials (Pittler and Ernst, 2000). However, it is interesting to note that such usage is not completely new. Felter (1905) notes kava's application, *inter alia*, for treating neuralgia, dizziness, and despondency. The herb has a particular value for treating agitation and anxiety (Spinella, 2001) when other nervines have proved to be ineffective.

Clinical trials have been reviewed recently by Pittler and Ernst (2000) who stated that, for treating anxiety, kava's superiority over placebo was suggested by all seven trials under review and that, for the three trials included in the meta-analysis, there was a significant reduction in score on the Hamilton Anxiety Scale. The clinical trials were all carried out in Germany where kava is prescribed by physicians and sold over the counter in pharmacies for treating anxiety and insomnia. A recent review (Loew, 2002) listed nine double-blinded, randomized controlled trials, involving 808 patients, and stated that kava was significantly superior to placebo for treating symptoms associated with anxiety. These trials used a range of products standardized on 15%–70% kavalactones, providing a daily dosage of 60–210 mg per day of kavalactones. The use of kava is being increasingly advocated as an alternative to benzodiazepines for treating anxiety and has been tested in at least one trial. (Loew, 2002). The trial was 28 days long and involved 61 people. And, for example, De Leo et al. (2001) showed a significant relative decrease in anxiety in a double-blinded randomized trial on 40 menopausal women when

kava was combined with hormone replacement therapy. This trial lasted for 6 months and the dosage of kava extract was 100 mg per day (containing 55 mg of kavain). It has been claimed that the German Federal Institute for Drugs and Medical Products, (German initials are BfArM), cited doubts about kava's efficacy for treating anxiety as one reason for starting an investigation on the herb (Anonymous, 2001). Surprise was expressed in Germany for this reason because it was claimed (Anonymous, 2001) that a recent randomized controlled trial awaiting publication had demonstrated kava's efficacy for this use at doses that conform to the Commission E monograph on the herb (Blumenthal, 2000).

The modern use of kava as a nervine is in accordance with its traditional usage in the South Pacific. Kava drinkers report a sense of relaxation and tranquillity and manifest a sociable attitude (Chanwai, 2000). The herb is used as a social and ceremonial drink among men in Polynesia. In modern times, as the influence of the Christian missionaries decreases, kava's use has become more widespread and frequent. For instance, Kava is an important part of social life in Fiji. Fijian spiritual leaders are called *dauvaguna*, the literal translation of which means "expert at drinking kava." (Greenwood-Robinson, 1999). Kava is not addictive and does not seem to produce the violent antisocial effects that alcohol produces (Lebot et al., 1997). However, there are serious concerns in Australia (Clough, et al., 2000) about the herb's abuse as a recreational drug when it is used to excess. It has been associated with inactivity, confusional states, and general ill-health, possibly as a result of associated malnutrition caused by irregular eating habits (Chanwai, 2000). In Aboriginal communities malnutrition is not uncommon and this association is considered to be unproven.

WHAT IS KAVA?

Root bark and root of kava are used, either fresh or dried, for its preparation.

Based on an archaeological study of characteristic drinking bowls, it has been proposed that the herb was first domesticated in Polynesia more than 2000 years ago (Green, 1974 [cited

in Lebot et al., 1997]). A comprehensive survey by Lebot and Levesque in 1989 (cited in Lebot et al., 1997) suggests that kava was originally domesticated in the Vanuatu islands.

Kava is now obtained from a wide range of cultivars in the South Pacific. The plant is always propagated vegetatively from stem cuttings as it does not reproduce via fertilization methods. There are many cultivars and new strains continue to be developed by Polynesian farmers because each strain is considered to have different psychoactive effects.

In recent years, there has been increasing pressure on the market because of the increased worldwide demand for kava. In 1998, it was among the top-selling herbs in the United States, with a turnover of \$8 million, representing a growth rate of 473% (Pittler and Ernst, 2000). It is possible that the current hepatotoxicity problems are, to some extent, a consequence of poor quality control caused by a rapid and extraordinary increase in the size of the market (Murray, 2000).

There are also concerns that intensive cultivation and harvesting may affect the quality of the product (Aarlbjerg, 1999). However being that a range of products is implicated, this is unlikely to provide a satisfactory explanation for all the reported adverse reactions. It is hoped that the BfArM will release relevant data about the source and quality assurance of the kava supply in due course.

KAVA PHARMACOLOGY

Kava is a well-researched herb. The crystalline resin was first isolated in 1857 by a French naval pharmacist and a detailed monograph was published in 1886 (Lewin, 1886 [cited by Lebot et al., 1997]). The kavalactones are considered to be the active constituents and have been shown in animal studies to have a sedative action (Hansel, 1996), although the mechanism is unclear (Spinella, 2001). The kavalactones are found in the resinous portion (5%–9%) of the plant material and are poorly soluble in water.

Kavalactones are 4-methoxy-2-pyrone with phenyl or styryl substituents at the 6th position (Lebot et al., 1997). Total kavalactone content

varies from 3% to 20% dry weight. Eighteen lactones have, so far, been isolated (He et al., 1997) with the following six compounds (including four chiral enantiomers and two achiral enantiomers) being considered most important (Haberlain, 1997; see Fig 1):

- Chiral enantiomers:
 - (1) (+)-kavain
 - (2) (+)-dihydrokavain
 - (3) (+)-methysticin
 - (4) (+)-dihydromethysticin
- Achiral enantiomers:
 - (5) yangonin
 - (6) demethoxyyangonin.

TRADITIONAL PREPARATION TECHNIQUES

Kava is traditionally prepared in the South Pacific by grinding and mixing the root or root bark with cold water. This makes an emulsion that is a suspension of the resinous constituents in water (Lebot et al., 1997). The herb is also prepared as an emulsion (also traditionally prepared without heating) in coconut milk (Johnson, 1999). The efficiency of extraction of the active constituents, which is measured by kavalactone extraction into water, varies considerably (Murray, 2000) but is higher from fresh material than from the dried plant. Kava consumed in Vanuatu is reputed to be the strongest anywhere in the South Pacific. The islands of Tanna and Pentecost are especially noted for their potent brews. It is thought that part of this increase in potency is the result of preparing the drink from the raw fresh roots, whereas in Fiji and elsewhere, it is made from dried rootstock (Greenwood-Robinson, 1999).

MODERN PREPARATION TECHNIQUES

The bioavailability of kava constituents varies substantially, depending on the method of extraction (Hansel et al., 1994 [cited in Schulz et al., 1997]; Loew, 2002). Kava is predominantly available in Germany as a so-called concentrated standardized extract that is designed to maximize extraction of the kavalactones.

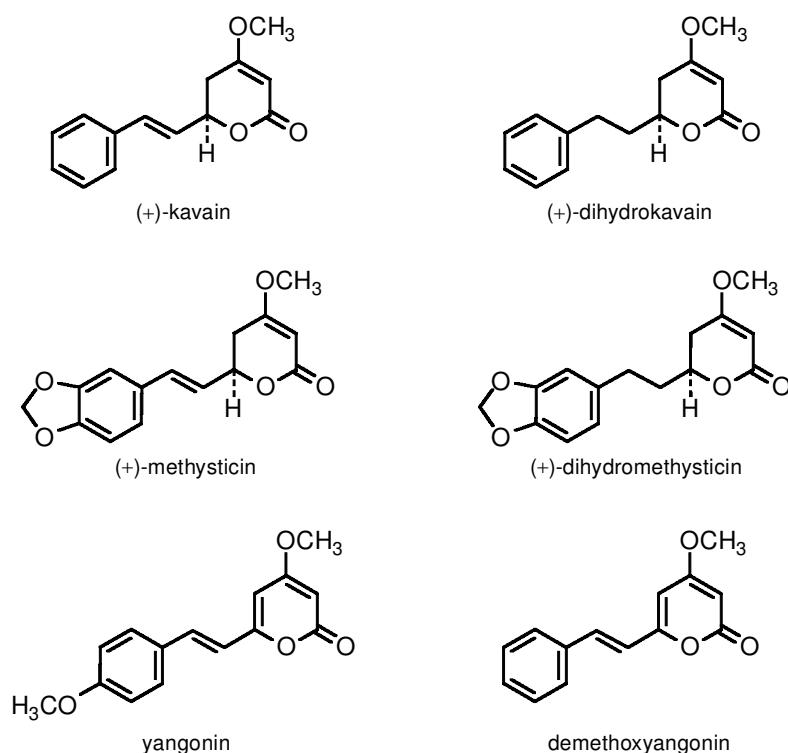


FIG. 1. Kavalpyrones of kava (*Piper methysticum*). Per Haberlein et al., 1997.

Schulz noted that, to create these concentrated standardized extracts, kava is dissolved in a high percentage of an ethanol–water mixture to obtain extracts containing approximately 30% kavalactones or, alternatively, using an acetone–water mixture to obtain extracts containing approximately 70% kavalactones. Whitton, Whitehouse, and Evans (Appendix 1) make the same point about enhanced kavalactone extraction using a high ethanol or acetone medium but detail somewhat different extraction values. Both types of products have a herb-to-extract ratio of approximately 12–20:1 (Schulz, 1997). The dosage recommended by the German Commission E is expressed as the equivalent of 60–120 mg of kavalactones per day (Blumenthal, 1998).

The preparation methods used for standardized products are highly technical and extraction rates vary (Kubatova, et al., 2001) depending on the solvents used and the temperature at which the products are prepared. As Whitton et al. propose (Appendix 1), both efficacy and safety may depend on the kavalactones remaining in their natural forms and on the extraction of the other natural constituents of the plant.

Varying extraction techniques and preparation methods may result in an unnatural variation in the relative concentration of each lactone or in production artifacts that may be pathologic to the liver. It should be noted that some commercial kava products may also contain synthetic racemic kavain that may have other characteristics than the naturally occurring product has. It is clear that these technical matters related to extraction techniques require further elucidation.

Proponents of concentrated standardized products assert that they provide an effective dose within a consistent range. The traditional water-based kava preparations of the Polynesian peoples and low-alcohol kava tinctures used by herbal practitioners have been considered to be unreliable because the concentration of active constituents is relatively low and varies from kava batch to batch. However, there are four relevant counterarguments:

- (1) The whole range of the constituents may produce a more effective and safe medicine (Williamson, 2001).
- (2) Some constituents, not necessarily considered active, may enhance the safety of the medicine (Appendix 1).

- (3) Definitive isolation of the active constituent is elusive in other medicinal plants, such as *Hypericum perforatum* (McIntyre, 2000; Barnes et al., 2001).
- (4) Herbal practitioners rely on the synergy between a whole range of constituents in the herb or herb within a herbal prescription, which is individually prescribed for a patient. This positive interaction may also have the benefit of keeping levels of any one constituent below the safety threshold.

LOW-ALCOHOL TINCTURES

The Traditional Medicines Evaluation Committee (TMEC) strongly advocates the use of extraction techniques that closely approximate those traditionally used in Polynesia. This would require the use of low-alcohol tinctures made by the traditional cold maceration processes common to U.K. tincture making. The reasons for this opinion are set out below; they have also been explored by Whitton et al. (Appendix 1).

Tinctures used by herbal practitioners are prepared by macerating dried kava in a mixture of water and ethanol. It has been shown that such extracts using 25% ethanol/75% water contain up to 30 times fewer kavalactones than the concentrated standardized preparations (Appendix 1). The traditional preparation method, using a mixture of 25% ethanol/75% water, extracts a wider range of the natural kava constituents, (Appendix 1).

DOSAGE AND OVERDOSAGE

Assuming a 1:5 25% tincture and an upper limit of 20% kavalactones in the dried herb (concentrations stated as 3%–20%; see section on Pharmacology below), then 500 mL of the herb would contain $(100 \times 0.2 \times 0.15) = 3$ g (3000 mg) of kavalactones. In addition, assuming a daily dosage of 5–10 mL of the 1:5 25% tincture, the daily dose of kavalactones amounts to a maximum of 30–60 mg. If the concentration of kavalactones were lower, for example at approximately 10%, as appears to be the case with regard to Australian kava dis-

cussed by Clough et al. (2000), then this dosage falls to 15–30 mg per day. It is noteworthy that the maximum daily dosage here is equivalent to the minimum daily dosages of the 60–210 mg kavalactones given in clinical trials of kava conducted in Germany.

Although standardized extracts provide a higher dosage of kavalactones than low-alcohol tinctures, overdosage in itself is unlikely to be the cause of hepatotoxicity. Strong evidence for this is the fact that kava is taken daily at high doses as a normal part of daily life in large areas of the South Pacific. Indeed, some of the accounts of high kava intake are remarkable. For example Chanwai (2000) described the case of a man who was admitted to a hospital after an overdose but “slept off” his symptoms and admitted to consuming up to 40 bowls of a kava preparation per day for the last 14 years. In Australia, missionaries introduced kava to the aborigines in the 1980s as a substitute for alcohol and it is claimed that this has led to abuse of kava. Clough et al. (2000) discussed this concern and reviewed twelve studies on the amount of kava used. The researchers found that social setting appears to determine the amount used, with lone drinkers consuming much more than people who enjoy kava in a family group. The researchers described normal use of kava in the Northern Territory as being 37 g of kava powder (containing approximately 3800 mg of kavalactones) per hour with heavy consumers using approximately 610 g per week, prepared as a drink. The incidence of serious illness resulting from hepatotoxicity associated with regular kava usage would surely have been observed by the medical services in Polynesia and Australia if overdosage of kavalactones were the main cause of hepatotoxicity.

UNTOWARD EFFECTS

There is a justified concern in Europe that idiosyncratic hepatotoxicity associated with using some herbal medicines may not be identified because the population that takes herbal medicines is not large enough to produce sufficient cases for the association to be noted. But the fact that kava remains in traditional usage to such a wide extent is a powerful argument

that idiosyncratic hepatotoxicity would have been noted.

Two postmarketing observation studies in Germany each on more than 3000 people were cited by Pittler and Ernst (2000) in addition to the abovementioned clinical trials. In these observational studies, the rate of adverse events was 2.3% (with a daily dose of 120–240 mg of kavalactones) and 1.5% (with a daily dose of 105 mg of kavalactones). The most frequent adverse reports were gastrointestinal complaints, allergic skin reactions, headaches, and photosensitivity.

There is evidence in the South Pacific of a characteristic kava-induced skin disease, a scaly rash that is suggestive of ichthyosis—a condition called “kava dermatopathy” (Ruze, 1990). Although the skin becomes yellow, the description does not suggest an underlying hepatic condition in that the patient remains well, the rash is not itchy, and the condition is ameliorated without treatment if heavy use of kava is reduced.

The German and Swiss reports cited by the BfArM are of concern because there have been previous reports of hepatotoxicity associated with the use of some medicinal plants (Larrey, 1997). The kava case reports from the BfArM (see Appendix 2) include all three of the main forms of acute damage that can result from adverse drug reactions: (1) necrosis; (2) drug-induced hepatitis; and (3) cholestatic hepatitis (Hodgson and Levi, 1997). This suggests that there is a range of causes rather than just one cause in these cases. The BfArM case reports have been circulated worldwide and are currently being evaluated by government agencies in Europe, Australia, Canada, the United States, and elsewhere. We have received a number of informal case assessments from these sources that cannot be specifically cited because of their confidential status. To achieve transparency and encourage a full debate about kava, however, the BfArM cases are evaluated in the section entitled Discussion of Cases Reported by the BfArM.

CRITERIA FOR ASSESSING THE CASE REPORTS

A recent review of the information available on the case reports (Schmidt and Nahrstedt,

2002) is supported by details of the case reports on the Web site of the University of Muenster (www.uni-muenster.de/chemie/pb/kava/analyse.html)

The criteria for causality assessment of adverse reactions used are as follows (Edwards and Aronson, 2000):

Probable is defined as:

- A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration and that cannot be explained by coincidental or concurrent disease or other drugs or chemicals
- The response to withdrawal of the drug (dechallenge) should be clinically plausible
- The event must be definitive, pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Possible is defined as:

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug but that could be explained by concurrent disease or other drugs or chemicals
- Information on drug withdrawal may be lacking or unclear.

Unlikely is defined as:

- A clinical event, including a laboratory test abnormality, with a temporal relation to the administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Unassessable is defined as:

- A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.

DISCUSSION OF CASES REPORTED BY THE BfArM

The cases discussed below are analyzed and categorized by common factors of note, with our own assessments.

(1) Cases of most concern

This group includes five cases: 10; 13; 16; 18; and 28. According to the assessments made by various government agencies, these cases cause the most concern and are often cited as being *probable*. For this reason, these cases are dealt with first. As discussed below, most—if not all—of these cases have associated factors that put this *probable* categorization into question.

Case 10. This case described necrotizing hepatitis in a 39-year old female patient with positive reexposure (Strahl, et al., 1998). During the first period that the kava product was taken, an oral contraceptive and paroxetine were concomitant medications. It appears that paroxetine was not the only antidepressant taken by this patient who also occasionally took St. John's wort (*Hypericum perforatum*). The Executive Summary issued by the Bundesverband der Arzneimittel Hersteller e.V. (BAH) and Bundesverband der Pharmazeutischen Industrie e.V. (BP) (see Appendix 3) stated: "A causal relationship with kava cannot be excluded, but the patient's history and a potential preexisting liver damage must be taken into account. In addition, the kava preparation used was not identified by the physician."

Moreover, in this case, taking paroxetine in combination with an oral contraceptive may well have led to overburdening the liver, a situation that could have been exacerbated by taking a kava preparation. Schmidt and Nahrstedt (2002) suggested that this case may be associated with an immunologic reaction. After reviewing all of the cases in detail, Schmidt and Nahrstedt (2002) concluded that this is the only case for which there was sufficient information to make an association with kava appear *probable* and for which the dose of kava also conformed to that recommended by the Commission E monograph (Blumenthal, 2000). However, as discussed below, Russmann et al. (2001) tested this patient for CYP2D6 and, as in Case 16, found this patient to be CYP2D6 deficient, which appears to have made her particularly vulnerable to the cocktail of drugs she was taking. Given the complicating features of this case, we submit that this case should be classed as *possible* rather than *probable*.

Case 13. This was a case of a 62-year-old woman with jaundice. The BfArM table (see Appendix 2) noted, regarding concomitant medication, that there was "none denoted" but it was claimed that concomitant medication did exist but was "unknown." The insufficiency of data provided for this case was highlighted by BfArM's warning note: "No medical message!" In addition, it should be noted that no details of the dosage of kava or period of its administration were apparently recorded for this case. This is clearly insufficient information on which to base a *probable* assessment.

Case 16. This case concerned a 33-year-old woman with jaundice. The woman was recorded as having taken an overdose of alcohol measured at 60 g (Russman et al., 2001) and then analgesics, including paracetamol, following this alcohol binge. Despite the massive intake of alcohol, a liver biopsy indicated that a drug rather than an alcohol induced toxic genesis. However, this case, like that of Case 10 above, was discussed by Russman et al. (2001), who demonstrated afterward that this patient was shown to be CYP2D6 deficient which (as discussed below) seems to be a risk factor for the hepatotoxicity that was ascribed to kava. We submit that, given these circumstances, this case should be considered *possible* rather than *probable*.

Case 18. This case concerned a 50-year-old man who had necrosis leading to a liver transplant. This patient took a product manufactured by acetone extraction at a dose delivering 210–280 mg of kavalactones per day for 1.5 months, "moderate alcohol" ("moderate" is not defined by BfArM), evening primrose (*Oenothera biennis*), and a yeast preparation. The dosage of kava was well above the German Commission E recommended dose of kavalactones (Blumenthal, 1998). It was also recorded that 500–1000 mg of paracetamol was taken by this patient shortly before transplantation. The combination of paracetamol and alcohol plus the very high dose of kava extracted in acetone taken by this man casts serious doubts on the assessment of *probable* in this case.

Case 28. (BAH) This case concerned a

woman, age unknown, with hepatitis. This case is hard to assess because neither the patient's age nor diagnosis was given and the woman was taking eleven medications, including estradiol valerate, acetylcysteine, losartan (which is rarely be associated with hepatitis), and meprazole (which can be associated with liver disease although this is rare). Omeprazole is metabolized by the polymorphic CYP2C19, which is absent in 3% of Caucasians (Flockhart et al., 2000). The woman was also taking echinacea (*Echinacea purpurea*) and five products that appeared to be for upper respiratory problems. It should be noted that this patient was taking synthetic kavain not kava. A comment from BfArM concerning this case noted "recurrence of the hepatic side-effects," which has evidently been interpreted by some authorities as being equivalent to a "positive rechallenge." Whether or not this was actually so was not clear from the data supplied. It appears (Schmidt and Nahrstedt, 2002) that Case 28 has been published as two cases with slightly different details. This is confusing, and considering that the woman was taking 11 other medications together with a synthetic kava (which, we submit, is not equivalent to natural kava) and that no diagnosis of her condition was supplied, this calls the assessment of *probable* in this case into question.

(2) Cases associated with taking synthetic kavain

In this category there were 4 cases: 1; 2; 19; and 28.

In each of these cases, the patients concerned were taking a product made from synthetic kavain. Although, the outcome was hepatitis in all four cases, kavain cannot be equated with the naturally occurring form of kava, which contains many other constituents that may play an important role in ensuring the safety of this herb. Therefore, we submit that no inference should be drawn from these cases. Traditional usage should not be taken as evidence for safe usage of synthetic products.

(3) Patients who were taking oral contraceptive pills or hormone replacement therapy (HRT) together with drugs that can also be associated with liver damage

The cases in this category were: 4; 10; 12; 20; 21; and 28.

Cholestatic jaundice associated with use of estrogen-containing medications is extremely rare (Lindberg, 1992) but does occur. In these 6 cases, the women were also taking drugs that can also be associated with jaundice.

Case 4. This case involved a 39-year-old woman with jaundice. She was on diazepam, 10 mg, PRN, for 6 months. Some authorities called this case *possible*. Our assessment is that the case is *unassessable*.

Case 10. This case involved a 39-year-old woman with necrotizing hepatitis. For a detailed assessment, see above.

Case 12. This case involved a 37-year-old woman with hepatitis. She was on 150 mg of diclofenac via intramuscular injection. Hepatotoxic reactions associated with nonsteroidal anti-inflammatory drug use are extremely rare and concomitant exposure to other hepatotoxic drugs is considered to be an important factor (Bareille et al., 2001). This case of hepatitis is difficult to interpret because it occurred in Brazil and because "reexposure was said to be negative for all three drugs." We regard this case as *unassessable*.

Case 20. This case involved 50-year-old woman with necrosis, who had a liver transplant. She had a 20-year history of combined oral contraceptive use but had changed months earlier to estradiol valerate (which was apparently taken alone) as HRT. She had also started glimepiride 8 months earlier. This is used for treating type II diabetes and is rarely associated with cholestatic jaundice and liver failure. We regard this case as *unlikely*.

Case 21. This case involved a 22-year-old woman with necrosis, who had a liver transplant. This woman had changed from Valette (Jenapharm GmbH, Jena, Germany) (2 mg of dienogest and 0.03 mg of ethinlestradiol) to Pramino (180/215/250 mcg of norgestimate and mcg 25 of ethinylestradiol). She also took rizatriptan, if required, for migraine relief. Rizatriptan should be used with caution in hepatic impairment and avoided if a patient has severe liver disease. Some authorities consider this case as being *possible* but our assessment

is, in view of the other medications taken, is that this case is *unassessable*.

Case 28. This case involved a woman, age unknown, with hepatitis. This case is discussed at length above. As noted above, this patient was taking synthetic kavain not kava.

(4) *Patients who were taking drugs that can be associated with liver damage*

There were ten cases in this category: 1; 6; 9; 14; 15; 17; 19; 23; 26/27; and 29.

Case 1. This case involved a woman, age 69, with cholestatic hepatitis. She was taking pentoxifylline (which can be associated with intrahepatic cholestasis) and a diuretic including the potassium-sparing triamterene (which can be associated with jaundice). As noted above, this patient was taking synthetic kavain not kava. We consider this case *unassessable*.

Case 6. This case involved a woman, age 50, with hepatitis. She was taking frusemide (which can be associated with cholestatic jaundice), triamterene, atenolol, and a large dose of terfenadine (300 mg). The recommended dose of terfenadine in the British National Formulary (March 2001) is 60–120 mg. The Formulary recommends avoiding this drug in patients who have hepatic impairment and also says to “avoid concomitant administration of drugs liable to produce electrolyte imbalance such as diuretics” (British National Formulary, 2001). Despite this warning, this woman was also taking the diuretic frusemide. The Interkantonalen Kontrollstelle der Schweiz of Switzerland considered this case of hepatitis to be caused by terfenadine. And, although some authorities regard this case as *possible*, our assessment is that this case is *unlikely*.

Case 9. This case involved an 81-year-old woman who had liver failure and subsequent death. She was taking hydrochlorothiazide (which can occasionally be associated with intrahepatic cholestasis). However, according to Schmidt and Nahrstedt (2002), there was evidence of chronic alcohol abuse and they reported that the autopsy showed chronic pancreatitis that was characteristic of alcohol abuse. The autopsy report (Schmidt and

Nahrstedt, 2002) apparently said that the symptoms must have occurred over a period of at least 18 months. The report conceded that “hepatic impairment by alcohol [was] not excluded.” In these circumstances, it seems entirely reasonable to claim that this case is unrelated to kava use. We regard this case as *unlikely*.

Case 14. This case involved a 33-year-old woman with hepatitis. Cisapride may have been taken (which can cause reversible changes that show in liver-function tests). Cirrhosis in a woman of 33 is an unexplained finding and the detail in this case is inadequate to elucidate it. We consider this case to be *unassessable*.

Case 15. This case involved a 46-year-old woman with jaundice. She had been taking hydrochlorothiazide (which can be associated with intrahepatic cholestasis) for 5.5 months plus 80 mg of valsartan and 80 mg of propranolol per day. Some authorities regard this case as *possible* but we consider it to be *unassessable*.

Case 17. This case involved a 59-year-old woman with jaundice. She had taken 100–200 mg of celecoxib, a cyclo-oxygenase-2 inhibitor, per day. According to the criteria for causality assessment of adverse reactions, some authorities consider this case to be *possible* but our assessment is that it is *unassessable*.

Case 19. This case involved a 21-year-old woman with hepatitis. She was taking pantoprazole (which, as with omeprazole, can be associated with liver disease). She was also taking paracetamol and metoclopramide and had overdosed on kavain. More detail is needed on other medical conditions suffered by this patient in order to interpret this case. It is suggested by Schmidt* that this woman was using up to 10 tablets per day of the product (the recommended dose is up to 6 tablets per day) and that there was apparently a discussion in her medical record file that she may also have used Ecstasy (substance that has been associated with

*Personal communication from M. McGuffin to M. McIntyre; available as an online document at ehpa@globalnet.co.uk

fulminant hepatic failure). This case appears to be *unassessable*.

Case 23. This case involved a 35-year-old woman with jaundice. According to the BfArM (see Appendix 2), this patient also took paracetamol but no dosage or details were provided. This case, and case 25 in the BfArM listing, appear to be the same case. Both cases have been labeled as *possible* by some authorities but, given the lack of information about the dosage of paracetamol and the apparent confusion regarding cases 23 and 25, we submit that the only logical assessment is *unassessable*.

Case 26/27. This case involved a woman who was either 38 or 39 years' old with hepatitis. It appears that the two cases have been duplicated (Schmidt and Nahrstedt, 2002). The confusion with this case is another example of inaccurate data provided by the BfArM. Information regarding these cases (or case?), depending on whether the two reports concern the same woman, is unclear. Penicillin can be associated with hypersensitivity and cholestatic jaundice but the information given is inadequate to make any meaningful assessment. For this reason, we class this case as *unassessable*.

Case 29. This case involved a 60-year-old woman who had a liver transplant. This woman was taking piretamide (which is a loop diuretic). Frusemide, another loop diuretic, can be associated with cholestatic jaundice. According to the BfArM chart (see Appendix 2), she was also taking a sympathomimetic drug, etilefrin. The dosage of kava varied but was up to 480–1200 mg per day (Schmidt and Nahrstedt, 2002), which is up to ten times the German Commission E maximum recommended dose (Blumenthal, 1998). Although some authorities have regarded this case as *possible*, in view of the marked overdosing of kava and the concomitant medication, this case can hardly be said to be a reflection on the proper therapeutic use of kava.

(5) *Cases in which drugs not associated with liver damage, herbal medicines, or dietary supplements or kavain alone were taken*

This category had eight cases: 2; 7/8; 11; 13; 22; 24; and 25.

For these cases, detail was limited and the BfArM did not implicate any other drugs or medications (although this may not be the case).

All patients in this group, apart from the patient in Case 7/8, for whom no information was given, were reported to have made full recoveries. In some of these cases, it is not clear whether the patients were ill or whether these cases merely recorded raised liver-function enzymes.

Case 2. This case involved a 35-year-old man with cholestatic hepatitis. Concomitant medication was "unknown." Apart from Cases 18 and 30, this is the only case for which it is possible that no other concomitant medication was taken but there is a marked lack of information for this case. As noted above, this patient was taking synthetic kavain not kava. We regard this case as *unassessable*.

Case 5. This case involved a woman who was either 68 or 69 years' old with cholestatic hepatitis. She was also taking a St. John's wort (*Hypericum perforatum*) product, which has been associated with CYP3A4. A biopsy showed "immunologic hypersensitivity." This case may be regarded as *possible* but, in view of the immunologic hypersensitivity, it may well have been an idiosyncratic event that was not necessarily associated with kava usage.

Case 7/8. This case involved a woman or two women, ages 72 and/or 75, with cholestatic hepatitis. These two cases appear to be actually one case. The woman was taking two herbal/vitamin products, one of which included 0.6 mg of kavalactones. Given the confusion involved, these "cases" must be regarded as *unassessable*.

Case 11. This case involved a 59-year-old woman who was taking hyoscine butylbromide as a suppository. Schmidt and Nahrstedt (2002) commented that, according to additional information obtained from the BfArM, it is uncertain as to whether this patient was taking a kava product at all. We regard this case as *unassessable*.

Case 13. This case involved a 62-year-old woman with jaundice. See above for the discussion of this case. It does appear that there was concomitant medication but no details of this or of the kava dosage are available. This makes interpretation impossible; consequently, we regard this case as *unassessable*.

Case 22. This case involved a 34-year-old woman with hepatitis. She was taking L-thyroxine. No information is available on her viral serology, differential diagnosis, or alcohol intake. We regard this case as *unassessable*.

Case 24. This case involved a 47-year-old woman who had raised liver-function as shown on a test. She had a high intake of fish-oil. The report stated that this patient's liver enzymes returned to normal when she stopped taking fish oils but, again, the detail is insufficient. However, this case appears to support the safe use of kava because report stated that the patient was "restored to health after discontinuation of the concomitant medication and continuation of the (kava) medication." We consider this case to be *unlikely*.

Case 25. This case involved a 34-year-old woman with hepatitis. According to the information provided by the BfArM, this woman was just taking *Hypericum perforatum* concomitantly. There is confusion about whether this is the same case as Case 23 and that, as recorded by BfArM (see Appendix 2), paracetamol was indeed a concomitant medicine. This case must be classed as *unlikely*.

(6) Cases associated with an overdose of alcohol

This group included two cases: 16 and 9.

Case 16. This case involved a 33-year-old woman with jaundice. This case is discussed at length above because some authorities regard this case as being *probable*. The woman took an overdose of alcohol (recorded as 60 g). This case was described in detail by Russman et al. (2001) because the woman was deficient in CYP 2D6, which, as previously noted, may have made her vulnerable to the mixture of kava, alcohol, and paracetamol (which were taken for

hangover symptoms). In these circumstances, as stated above, this case is unlikely to be *probable*. We believe it to be *possible*.

Case 9. This case is discussed in subsection 4 above.

(7) Cases not associated with other drug usage

This group included two cases: 18 and 30.

These final two cases involved men, both of whom required liver transplants and both of whom appeared not to have been taking other medications. For these two cases, more details on the medical histories is required for proper assessment.

Case 18. This case involved a 50-year-old man with liver necrosis and who had a liver transplant. This case is discussed in some detail above. The man took an 210–280 mg of an acetone preparation per day for 1.5 months. He also had a "moderate alcohol" intake and took a yeast preparation. This is above the recommended dose of kavalactones. He may also have taken paracetamol (see above). This case is *unassessable*.

Case 30. This case involved a 32-year-old man with necrosis of the liver and who had a liver transplant. He took a product containing 240 mg of kavalactones per day for 3 months and occasionally a valerian (*Valeriana officinalis*) product at night. This, too, was above the recommended dose of kavalactones. This case cannot be evaluated fully because of lack of detailed documentation regarding the man's medical history or the presenting disease and so must be categorized as *unassessable*.

CYTOCHROME p450 METABOLISM OF XENOBIOTICS AND CYP2D6 DEFICIENCY

In most of these cases, the patients were also taking drugs concomitantly. Assuming that the medications were responsible for the adverse events, and not some other factors, such as other disease or excessive use of alcohol, it is possible that the hepatotoxicity was caused by the

conventional drugs, by the kava, by both the drugs and the kava, or mainly by the drugs with the kava as a cofactor. However, in assessing these cases, one should take into account the apparent increased risk of adverse effects on the liver where kavalactone concentration is enhanced in a product. In all cases cited by the BfArM, the affected patients appear to have been taking concentrated standardized products, which, in no way, relates to the traditional water-based or low-alcohol extracts that have not been associated with comparable adverse events. In any case, upon analysis of all relevant factors, the number of cases cited by the BfArM that can actually be attributed to kava is so low that the only logical conclusion that can be drawn is that kava has a low level of incidence of adverse events. Interestingly, Schmidt and Nahrstedt (2002) came to much the same conclusion, stating that the relative incidence of adverse events is a fraction of that of others connected with anxiolytics, such as benzodiazepines.

Interindividual variability in cytochrome-p450 metabolism of xenobiotics

Kava may be regarded as a possible cofactor in some of these cases, but variable individual responses (interindividual variability) to drugs or herbs should also be taken into account in these cases. Interindividual variability in drug response is now increasingly recognized as a major cause of adverse drug reactions. Much of this variability is now ascribed to genetic differences in drug absorption, disposition, metabolism, or excretion. The variability that has been most investigated and that is considered to be of most significance is genetic polymorphism in drug metabolizing enzymes in the hepatocyte. This is considered to be an adaptive response to environmental challenge (Wolf and Smith, 1999) so it is not, in itself, surprising that individuals vary and failure to metabolize xenobiotics ("foreign" compounds, whether these be natural or synthetic) is associated with using medicines from natural or synthetic sources.

Cytochrome p450 (CYP) enzymes are mixed function microsomal mono-oxygenases that are located on the smooth endoplasmic reticulum

throughout the body, primarily in hepatocytes and in the wall of the small intestine. There are 12 families and a single hepatocyte can contain a range of CYP enzymes that metabolize a range of drugs. These CYP enzymes are responsible for phase I (oxidation, reduction, and hydrolysis) metabolism of a wide number of compounds and for transforming lipophilic drugs into more polar compounds that can be excreted by the kidneys.

Phase II of detoxification occurs if a product conjugates in the hepatocyte cytoplasm with the tripeptide glutathione. The resulting soluble compound is excreted via the bile or the urine. This conjugation is catalyzed by cytoplasmic glutathione S-transferases. Interindividual variations exist in the concentration of hepatocyte glutathione and in the relative concentration of individual glutathione S-transferases (Mannervik and Widdersten, 1995) and in levels of other compounds that are associated with drug metabolism.

CYP2D6 deficiency

Many CYP enzymes are genetically polymorphic and, thus, there is marked interindividual variation in drug metabolism (Wolf and Smith, 1999). CYP2D6 is one of the most extensively studied genetic polymorphisms. It is thought to cause much of the individual variations seen in drug responses, side-effects, and drug interactions (Poolup et al., 2000). Individuals may be poor (slow) metabolizers, intermediate, extensive (fast), or ultrafast metabolizers. In a Caucasian population 7%–9% of individuals are homozygous deficient in CYP2D6 and are, thus, poor metabolizers (Poolup et al., 2000). The incidence of CYP2D6 deficiency in Asian populations is 1% and it is thought that much ethnic variation in drug response is associated with CYP polymorphism (Poolup et al., 2000). Drug substrates for CYP2D6 include antidepressants, antipsychotics, beta-blockers (e.g., propranolol and antiarrhythmics), and several antidepressants (Fromm et al., 1997). A poor metabolizer is at risk of having adverse reactions if his or her rate of biotransformation is inadequate.

If xenobiotics are inadequately metabolized, they may make covalent bonds with DNA, RNA, nuclear proteins, or cytoplasmic proteins and

breakdown of function occurs within these cells. When this breakdown is above a certain rate, the result of this is damage to the hepatocyte leading to centrilobular necrosis (Kaplowitz, 1997).

As noted above, Russmann et al. (2001) discussed Case 16 in detail. It is noteworthy that the woman had restarted kava for 3 weeks after an initial course of treatment 2 months earlier and then became ill 3 weeks later after an overdose of alcohol. The woman was shown to be CYP2D6-deficient, using phenotyping with debrisoquine. The researchers then tested the patient who was delineated as Case 10, which was described by Strahl et al. (1998), and found that she was also CYP2D6-deficient. Strahl et al. (1998) argued that CYP2D6 deficiency is a risk factor for hepatotoxicity that is ascribed to kava.

This finding may help to explain the lack of hepatotoxicity as a result of kava being recorded in the South Pacific. Wanwirolmuk et al. (1998) tested the phenotypes of 100 persons of pure Polynesian descent using a debrisoquine probe and found a 0% incidence of CYP2D6 deficiency. The researchers proposed that, with regard to this factor, Polynesians strongly resemble Asian populations.

As stated, many antidepressants are metabolized by CYP2D6 and it is likely that using antidepressants with kava is not uncommon. Yet, only one of the above cases involved antidepressants, which suggests that CYP2D6 deficiency is more likely to be relevant than competition between CYP2D6 substrates.

This finding is significant but difficult to predict because most people are unaware of their CYP2D6 phenotype. It should be noted that when CYP2D6 deficiency occurs, use of kava products with enhanced kavalactones might have implications for the affecting the liver, particularly when a concomitant orthodox medicine or substantial amounts of alcohol are taken regularly. It is proposed that such risks are likely to be small if low-alcohol tinctures are used within the normal therapeutic dosage range.

RECOMMENDATIONS FROM TMEC

TMEC recommends that:

(1) Products made from synthetic kavain are

synthetic drugs not herbal-medicinal products and should be excluded from the analysis.

- (2) None of the cases cited by the BfArM involved traditionally prepared tinctures. In the light of evidence presented above and by Whitton et al. (Appendix 1), the safety of concentrated standardized products made from acetone extracts and high-alcohol concentrations needs reevaluation. Low-alcohol tinctures appear to provide a safe alternative. TMEC recommends adopting extraction methods that use 25% alcohol to ensure that the full spectrum of constituents is extracted, resulting in a substantially lower concentration of kavalactones, thus, ensuring kava's safe use as a medicine.
- (3) Consumers need to be informed that kava products should not be taken together with conventional medicines without the advice of a health professional. Even more importantly, consumers need to know that kava should not be taken without consulting a health professional if users have established histories of liver disease.
- (4) Maximum doses for kava should be set after consultation with interested parties.
- (5) Doctors, nurses, pharmacists, and other health professionals should be adequately informed about herbal medicines and possible herb-drug interactions (Jobst et al., 2000).

SUMMARY

The Executive Summary issued by two German pharmaceutical associations—Bundesverband der Arzneimittel-Hersteller e. V. (BAH) and Bundesverband der Pharmazeutischen Industrie e.V. (BPI) (see Appendix 3)—of their submission to the BfArM concerning kava stated that the causality in most of the reports is unclear because details, such as additional medication, patient history, and consumption of alcohol are not given "thus not permitting a sound evaluation of these cases." Schmidt and Nahrstedt (2002) noted that a number of the cases have been reported in the literature more than once with different data, including, as noted above, case 28, and, in particular, that

cases 7 and 8 are the same as are cases 26 and 27. The details of the case reports given are also at variance with regard to case 4 in which a different time before onset is given and inconsistencies also occur in cases 23 and 25 in which the time before the onset of the two cases is reversed. These discrepancies are unsatisfactory and undermine confidence in the accuracy and veracity of the information provided by the BfArM. It has also been claimed (Schmidt and Nahrstedt, 2002) that the case reports are not presented in accordance with European Union guidelines for adverse-event reports.

The BfArM document is deficient in other respects too. It is unclear whether the term "liver damage" refers to the results of a liver biopsy or to the finding of raised alanine aminotransferase (ALT) blood levels that are interpreted as indicating damage to hepatocytes in hepatocellular disease (Pagana and Pagana, 1999). However, in light of the need for the U.K. Committee on Safety of Medicines to make an informed decision on these cases, this paper endeavors to interpret the evidence as presented. Unless noted otherwise, references to possible drug-induced hepatotoxicity are taken from the *British National Formulary* (BNF), (March 2001).

ACKNOWLEDGMENTS

Thanks to Angela Grunwald for translating a number of German texts that provided valuable background for this paper.

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APPENDIX 1

**Response to Reported Hepatotoxicity of High Lactone Extractions of
Piper methysticum Forst. (Kava)**

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and CHRISTINE EVANS, B.Sc., Ph.D.³

Introduction

This paper (the result of work currently in progress) was produced in response to the reports by the German BfArM of possible hepatotoxic effects of kava (*Piper methysticum* Forst.) extracts that has led to concerns regarding the safety of kava products on sale in the United Kingdom. There have been thirty cases of hepatotoxicity reported to German and Swiss regulators including three transplants and one death allegedly associated with the use of concentrated standardized kava extracts.

In the Oceanic Islands of the South Pacific kava is drunk as an alternative to alcohol or for ceremonial purposes and studies have shown, in islanders who regularly drink up to ten times the recommended therapeutic dose, that the only recorded abnormality is a slightly raised gamma-glutamyltransferase (Barguil, 2001).

The analysis presented in this paper, based on as-yet-unpublished research by the authors, demonstrates the presence of glutathione in the traditional extract, which, it is postulated, may have a hepatoprotective effect. Concentrated standardized extracts do not contain glutathione (see below).

Extraction Techniques

In the Oceanic Islands, kava is traditionally prepared by macerating the root or root bark in a cold water and/or coconut milk solution. However, in the manufacture of concentrated extracts either ethanol (60% and above) or acetone (60% or above) is used as a solvent to obtain the maximum yield of kavalactones* that have been identified as the "active constituent."

Research Data (The Result of Work in Progress)*Analysis of kava extraction in different solvents*

Kava root was extracted in different solvents and analyzed by high performance liquid chromatography (HPLC) with diode-array detection. Different solvents were used to extract the kavalactones and their extraction is shown in Table 1.

The extraction was carried out by reflux percolation for 1 hour for each sample of 5% w/v *Piper methysticum* root. The resulting liquids then had their specific gravity and percentage of dry extract determined by the techniques described in the British Pharmacopoeia, (1999). The total kavalactones were measured by HPLC using an acetonitrile/water solvent gradient (Whitton, 2001).

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TABLE 1. EXTRACTION OF KAVALACTONES IN DIFFERENT SOLVENTS: SUMMARY OF RESULTS FOR TEN SAMPLES IN EACH SOLVENT

<i>Extract</i>	<i>% Kavalactones in dried extract</i>
Acetone extract	100
96% Ethanol extract	100
25% Ethanol	15
Water	2.97

Kavalactone standardized extracts are produced using a high acetone or ethanol concentration and are likely to contain only kavalactones and no proteins, amino acids, or sugars.

Further analysis identified one of the other compounds in the aqueous extract and in the 25% ethanol extract as glutathione by comparison to a reference sample obtained from Sigma-Aldrich (Poole, Dorset, United Kingdom).

Samples of commercially available kava extracts were examined and the ratio of kavalactones to glutathione was calculated; the results are shown below in Table 2 and Figure 1.

Importance of Glutathione in Kava Extracts

Kavalactones may cause hepatic stress, if not mediated by glutathione, and are usually metabolized in the liver by enzymes called lactone hydrolases (Schmidt et al., 1999). It can also be demonstrated *in vitro* that kavalactones combine with glutathione in a pH dependant reaction by placing a mixture of kavalactones and glutathione in a test tube and adding 0.1M of sodium hydroxide to adjust the pH to between 7 and 10. In the control solution of kavalactones alone in this solution, no change occurs. The same process is observed when cysteine is used instead of glutathione. This reaction is possibly nonreversible and causes the decolourization of the solution. This point is important as it shows that the lactone ring structures have been opened and, thus, changed into other as-yet-unknown compounds. The opening of the lactone ring renders the complex water-soluble and so it can be absorbed into the gut. This may bypass the phase I enzymatic detoxification pathway in the liver thus causing no depletion of intracellular glutathione in the hepatocyte. The pH range of this reaction renders it liable to occur in the duodenum and so most probably occurs *in vivo* between the kavalactone and the cysteine moiety of the glutathione molecule after the glutathione has been broken down to its constituent amino acids by the gastric enzymes.

It could be that the high concentration of kavalactones introduced by concentrated standardized extracts has the potential to saturate the enzymatic detoxification pathways resulting in undue stress on the liver. Glutathione has an essential role in the phase II conversion of kavalactones into excretable waste products, and thus glutathione is relevant in excess dosage of

TABLE 2. KAVALACTONE/GLUTATHIONE RATIOS
(RESULTS SUMMARIZED FROM TEN SAMPLES OF EACH TYPE)

<i>Sample</i>	<i>Kavalactone content (expressed as absorbance)</i>	<i>Glutathione content (expressed as absorbance)</i>	<i>Kavalactone/glutathione ratio</i>
Kava standardised extract powder (30% kavalactones) dissolved in 25% ethanol	4.031712e6	1.346769e3	1/0.0003
82% Ethanol extraction	3.168906e5	5.3813e3	1/0.017
25% Ethanol extraction (1 part plant to 3 parts solvent)	1.63689e4	1.88736e4	1/1.15
25% ethanol extraction (1 part plant to 1 part solvent)	2.49798e4	5.1525e4	1/2.2

e, napierian logarithm.

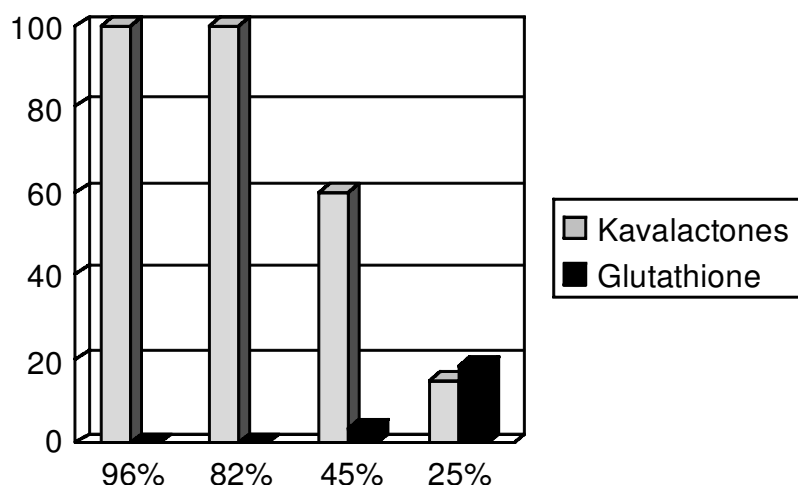


FIG. 1. Kavalactone and glutathione extraction (expressed as a percentage of dry extract) against ethanol percentage in solvent.

kavalactones. Glutathione is not soluble in ethanol concentrations above 50% (Merck Index, 1996). There has been relevant work on a related group of compounds, sesquiterpene lactones. It has been demonstrated that sesquiterpene lactones react with the sulfide group on the glutathione molecule in a reversible pH dependent reaction (Schmidt et al., 1999). The binding of the sesquiterpene lactones to the glutathione molecule allows for faster clearance by the lactone hydrolases present in the hepatocytes (Schmidt et al., 2001). It has been demonstrated that oral glutathione prevents toxicity from sesquiterpene lactones if administered at the same time (Lautermann et al., 1995). It has also been documented that oral glutathione has to be taken at the time of ingestion of the kavalactones in order to potentiate the metabolism of the kavalactones.

We have shown using *Acanthamoeba* that, when kavalactones are added to the growth medium, the organisms die rapidly. However, when the same experiment is carried out using a 50:50 mixture of kavalactones and glutathione no cell death occurs. It was found that no cell death occurred in concentrations of the glutathione/kavalactone mixture of 50 mg/mL whereas cell death occurred using kavalactones alone at concentrations of less than 1 mg/mL. Using photomicroscopy, cell death was assessed via visual criteria of cell movement and cell morphology. It is planned to repeat this procedure using hepatocyte cultures but, as the phase I and phase II pathways are common to most life forms, it is considered that these results could show that glutathione is indeed required for the metabolism of kavalactones.

Glutathione is present in adequate amounts in most cells in the body but some individuals can have a genetic deficiency (Lomaestro and Malone, 1995). In these cases, high doses of kavalactones will lead to rapid depletion in glutathione levels and result in free lactone exposure in the hepatocytes and consequent tissue damage (Zheng et al., 2000). Glutathione supplementation (taken orally) has been shown to correct the deficiency (Kidd, 1997). It is suggested that the glutathione molecule may not be absorbed intact but may be broken down into its constituent amino acids and regenerated within the hepatocyte.

It can be postulated that, as the reaction occurs *in vitro* without the presence of enzymes, the binding of the sulphydryl group of common to the glutathione and the cysteine moiety to the kavalactone may take place in the duodenum before absorption. This would allow the same pH effect as has been seen *in vitro* and allow the Michael type reaction (Merck Index, 1996) to occur. It has been demonstrated *in vitro* (in original research undertaken by the authors) that the addition of either glutathione or cysteine to kavalactones at a pH between 6.8 and 10.0 in an aqueous environment leads to the solubility of the kavalactones with decolourization of the solution when compared to the same process without the cysteine or glutathione.

The decolourization strongly suggests that the lactone ring has been opened in this reaction thus making the resultant compound water-soluble. This means that this reaction, which takes place without the presence of enzymes, can occur in the duodenum. This would lead to the absorption of the complex of cysteine/glutathione and kavalactone into the hepatocyte without putting stress on the phase I pathway and so no depletion of intracellular glutathione would take place. This suggests that the liver was able to cope with oxidative stress from other sources with no interference from the kava.

Previous experiments have been conducted with oral glutathione and acetaminophen (paracetamol) where no non-enzymatic pathway has been observed. These findings are readily explained by the different structural formulae of these compounds (Fig. 2).

It can be demonstrated that the cysteine moiety of the glutathione molecule binds via the Michael reaction to the oxygen atom in the lactone ring with the kavalactones. This opens the ring and leaves the double-bonded oxygen unit intact. As mentioned previously, the resulting conjugate is water soluble because of the presence of the thiol group from the cysteine. In the case of acetaminophen (paracetamol), this reaction cannot take place without the presence of the phase I enzymes as the molecule is cleaved at the amine (nitrogen) group in alkaline conditions (as the authors have demonstrated). This is quite possibly the reason why large doses (ten to fifty times the therapeutic dose of 60–120 mg per day) of the traditional kava extract have been shown not to cause hepatic damage whereas the standardized concentrated extract has been associated with these cases.

Another strong piece of evidence that the kavalactones may be moderated by other components in traditional use comes from the epidemiologic studies carried out in Arnhem Land in

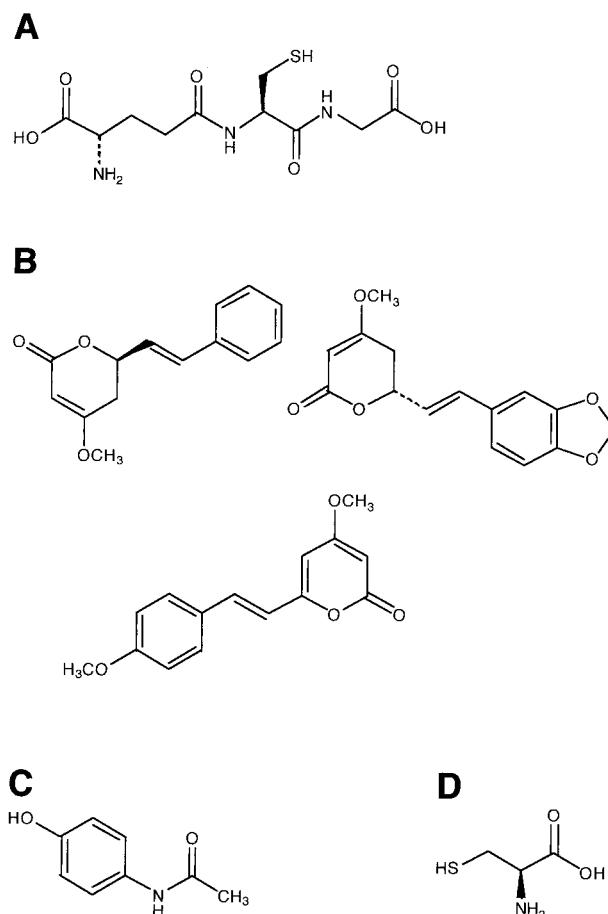


FIG. 2. Chemical structures of (A) glutathione, (B) kavalactones, (C) acetaminophen, and (D) cysteine.

the Northern Territories in Australia. These preliminary studies have found no evidence of liver damage in individuals who habitually ingest kava extracts equivalent to between ten and fifty times the daily therapeutic dose (60–120 mg) of kavalactones per day.*

Summary

Kavalactones are normally metabolized by lactone hydrolases, which are enhanced by the presence of glutathione.

Glutathione naturally occurs in kava in a 1:1 ratio with kavalactones and is likely to reduce the likelihood of potential lactone toxicity. In contrast to the traditional crude extract, standardized extracts contain no glutathione while containing up to 30 times the kavalactone concentration.

It appears that the high kavalactone in concentrated standardized extracts may deplete the reserves of glutathione in the hepatocytes which could result in liver damage. It would therefore seem prudent to limit the organic solvent level in the extraction of kava to 25% ethanol in order to ensure the preservation of the hepatoprotective effect of the glutathione. Tinctures made with 25% ethanol would appear to be safe as a result of this synergistic effect of the glutathione and kavalactones.

Conclusions

Traditional preparations have had many years of safe usage (Norton and Ruse, 1994) and toxicity has only been reported in Europe with concentrated standardized extracts (Escher et al., 2001).

This paper argues that there are significant differences between concentrated extracts and those produced by traditional methods that maintain a satisfactory ratio between glutathione and kavalactones. In traditional extracts, ratios of at least 1:1 kavalactone:glutathione should provide a safe product with hepatoprotective action. It would appear that glutathione has an important synergistic action in protecting the liver from potential lactone toxicity.

This study suggests that standardized herbal extracts which do not contain all components of the traditional plant extract may have a potential to induce hepatotoxicity in susceptible people (e.g., those taking concomitant orthodox medicines). It is proposed that tinctures manufactured using a traditional cold-maceration process (in 25% ethanol and 75% water) that is more nearly approximate to traditional water or coconut milk extracts, or raw plant material, are safe in normal subjects.

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APPENDIX 2

Case Reports as Analyzed by the German Federal Institute for Drugs and Medical Products
(the German BfArM): Circulated in November 2001

Identifier	Patient (age/gender) (f = female; m = male)	Dose	Indication	Timeframe (beginning of treatment reactions to first occurrence of symptoms)		Hepatic findings	Concomitant drugs	Notes
1	69/f	2 × 200 mg of synthetic kavain	Data missing	Data missing		Cholestatic hepatitis	ASS, dehydrosanol, Rentylin ^a	Recovered; hepatic side-effects described for all concomitant medications
2	35/m	2 × 200 mg of synthetic kavain	Anxiety states	Anxiety states		Cholestatic hepatitis	Data missing	Recovery after discontinuation
3	68/f	3 × 70 mg/d of acetone extract)	Data missing	Data missing		Increased liver enzymes; (present before beginning kava medication)	Data missing	Data missing
4	39/f	3 × 70 mg/d of acetone extract	Depressive neurosis	~4 years		Upper abdominal pressure; nausea; vomiting; icterus	Diazepam, ^a Gravistat, ^a L-Thyroxin	Recovery after discontinuation of all medications; hepatotoxicity also known for the concomitant medications
5	68/f	3 × 70 mg/d of acetone extract	Depressive emotional deterioration	~2 years		Cholestatic hepatitis; icterus	Neuroplant forte, ^a Maaloxan ^a if required	Recovery after 97 days; sporadic notifications of increased liver parameters under Maaloxan ^a
6	50/f	3 × 70 mg/d of acetone extract	Data missing	~2 months		Increased liver enzymes; liver cell-impairment; acute hepatitis with icterus	Teldane, ^a atenolol, Hydrotrix ^a	Hepatic side-effects also described for concomitant medications
7	72/f	Phyto- Geriatrikum ^a (with 25 mg dry extract with ethanol)	Data missing	~6 months		Jaundice; cholestatic hepatitis; liver-cell impairment	Eunova ^a	No hepatic side-effects known for concomitant medication
8	75/f	Phyto- Geriatrikum ^a (with 25 mg dry extract with ethanol)	Data missing	~2 years		Cholestatic hepatitis; hepatitis; liver-cell impairment	Eunova ^a	No hepatic side-effects known for concomitant medication
9	81/f	2 × 60 mg of ethanol extract	Anxiety/ restlessness	~9 months		Toxic hepatitis with liver failure; acute yellow liver dystrophy	HCT-isis 12,5, Cralonin Tr., ^a Bayotensin ^a (bis 1/98)	Exitus; seldomly icterus under hydro- chlorothiazide hepatic impairment by alcohol not excluded

10	39/f	60 mg/d?	Data missing	6 months and 14 days after reexposure	Severe hepatitis with confluent necrosis	Paroxetin, St. John's wort if required, hormonal ovulation inhibitors for 6 years Buscopan ^a	Recovery after 8 3 weeks; hepatic side-effects described for hormonal ovulation inhibitors
11	59/f	2 × 120 mg/d	Anxiety states	~4 months	Liver-cell impairment		Sporadic notifications of hepatic side-effects under Buscopan ^a
12	37/f	2 × 70 mg/d of acetone extract	Data missing	Data missing	Hepatitis	Microdiol ^a since 5 years, 2 × diclofenac IM	Recovery after 3 months; hepatic side-effects also known for concomitant medications
13	62/f	Ethanol extract	Data missing	Data missing	Liver-cell impairment	None denoted	No medical message
14	33/f	Ethanol extract	Data missing	~4 months	Bilirubinaemia; hepatitis, increased liver enzymes; cirrhosis of the liver	Cisapride	Hepatic side-effects also described for concomitant medication
15	46/f	Data missing	Data missing	Data missing	Severe liver damage with icterus	Propanolol, HCT, Valsartan ^a	Hepatic side-effects also described for concomitant medications
16	33/f	3 × 70 mg/d of acetone extract	Data missing	Data missing	Cholestatic hepatitis with icterus	1 × ~60g alcohol	Recovery after 6 weeks
17	60/f	70 mg/d of acetone-extract	Depression	Data missing	Increased bilirubin and transaminases; indolent icterus	Celecoxib	Recovery after 2 weeks; hepatic side-effects also known for concomitant medication
18	50/m	3–4 × 70 mg of acetone-extract	Nervous tension	~2 months	Acute necrotizing hepatitis; irreversible liver damage	Alcohol moderately, 1–2 × paracetamol; Nachtkerzensamenol ^a	Transplantation; notifications of hepatic side-effects under paracetamol exist
19	21/f	8–10 × 50 mg	Data missing	~2 months	Increased liver enzymes; jaundice; hepatitis	Paspertin ^a ; Pantoprazole; paracetamol; Basilikum-Tropfen ^a	Side-effects also known for concomitant medications
20	50/f	60 mg/d of ethanol extract	Stress states	~7 months	Fulminant liver failure	Amaryl ^a ; Glucophage S ^a ; Gravistat ^a followed by Klimonorm ^a	Transplantation; hepatic side-effects also known for Amaryl ^a (cholestasis; hepatitis) and Klimonorm ^a as well as Gravistat ^a (tumors of the liver; cholestasis; anicteric hepatitis)
21	22/f	2 × 120 mg of ethanol-extract	Nervousness; anxiety states; endogenous depression	~5 months	Necrosis; complete destruction of the parenchyma; fulminant liver failure	Maxalax ^a (if required); Pramino ^a (beforehand Valette ^a)	Transplantation; hepatic side-effects also known for Pramino ^a (tumors of the liver; cholestasis; anicteric hepatitis)
22	34/f	120 mg/d of dry extract with ethanol	Data missing	~3 months	Hepatitis; increased liver enzymes	Jodthyrox ^a	Recovery after discontinuation of kava medication; sporadic notifications of hepatic side-effects under Jodthrox
23	34/f	120 mg/d of ethanol extract	Data missing	~1 month	Increased liver enzymes; jaundice	paracetamol	Notifications of hepatic side-effects under paracetamol

(continued)

APPENDIX 2 (Continued)

Case Reports as Analyzed by the German Federal Institute for Drugs and Medical Products (the German BfArM): Circulated in November 2001

Identifier	Patient (age/gender) (f = female; m = male)	Dose*	Indication	Timeframe (beginning of treatment reactions to first recurrence of symptoms)	Hepatotoxic adverse drug	Concomitant drugs	Notes
24	47/f	Antares ^a 120; ethanol- extract	Data missing	~1 month	Increased liver enzymes	Fischolkapseln ^a	Restored to health after discontinuation of concomitant medication and continuation of Antares ^a -medication
25	35/f	Ethanol- extract	Data missing	~3 months	Hepatitis; increased liver enzymes	Hypericum capsules	Restored to health; no hepatic side- effects known for concomitant medication
26	38/m	Acetone extract	Data missing	~2 weeks	Liver-cell impairment	Penicillin-V ^a	No hepatic side-effects known for concomitant medication
27	39/m	70 mg/d of acetone extract	Data missing	~2 weeks	Liver-cell impairment	None	Data missing
28	Age not provided /f	Kavain extract	Data missing		Hepatitis	l-Thyroxine, Lorzaar ^a plus, Estragest ^b Pflaster, ^a Antra MUPS ^a	Recurrence of hepatic side-effects; hepatic side-effects also known for concomitant medications
29	60/f	Up to 480 mg/d of ethanol extract	Depressive emotional deterioration	~1 year	Fulminant liver failure	etilefrin-HCL, piretanid	Transplantation; sporadic notifications of hepatic side-effects under piretanid
30	32/m	~240 mg/d of ethanol extract	Restlessness	~3 months	Necrotizing hepatitis with insufficiency of the liver; metabolic- toxic-allergic drug damage	Baldrian ^a (occasionally)	Evaluation of the necessity for transplantation

^aInformation on generics, manufacturers, and locations were not provided for brand-name drugs.

Source: Appendix of a letter sent to participants in a step-by-step plan and copied to the Medicines Control Agency, which copied the letter to organizations on its consultation list. The letter was entitled "Hearing, stage II 7171-A-30646 67918/00-3390 drugs containing kava-kava (*Piper methysticum*) and kavaine, including homeopathic remedies with a final concentration up to D6." IM, intramuscular.

APPENDIX 3

Executive Summary Issued January 18, 2002, by the Bundesverband der Arzneimittel-Hersteller e. V. (BAH) and Bundesverband der Pharmazeutischen Industrie e.V. (BPI): Comments of BAH/BPI on the BfArM Letter of November 8, 2001, on Kava- and Kavain-Containing Medicinal Products

Executive Summary

On December 18, 2001, the BAH and BPI, the German pharmaceutical trade associations, submitted a statement to BfArM, the German health authority, on behalf of German kava manufacturers, subsequent to a letter from BfArM of November 8, 2001. The industry's statement comes to the conclusion that the presented data on the benefit/risk assessment of kava- and kavain-containing medicinal products do not justify the withdrawal of marketing authorisations. The companies already included risk information in their package leaflets and expert information at their own responsibility and consider control of patients applying kava products by a physician as an appropriate means of ensuring safe usage.

In particular, in most of the reported cases, the causality between kava intake and liver reactions is not clear because further medication was used which might have caused liver toxicity. In many cases, detailed information on the patients' history, co-medication, consumption of alcohol and further particulars are missing, thus not permitting a sound evaluation of these cases. Regarding clinical efficacy, there are placebo-controlled and reference-controlled clinical studies as well as open studies which demonstrate an improvement of symptoms in conditions of nervous anxiety, stress and restlessness.

Data on the Risk Assessment

The report published by Kraft et al. (2001) describes liver failure in a 60-year-old female patient who took a kava preparation in an amount up to four times of the recommended daily dose. Liver transplantation was required. Due to further medication containing piretanid and etilefrin which might have caused liver-related side effects, kava is unlikely to be the only cause of the side effect.

The case report published by Brauer et al. (2001) describes liver failure in a 22-year old female patient. Liver transplantation was required. Since the patient also took rizatriptan and oral contraceptives, which might have liver-related side effects, kava is unlikely to be the only cause of the side effect.

The case report published by Sass et al. (2001) describes a 50-year old female patient who took kava for seven months in a daily dose of 60 mg kavapyrones. She experienced a hepatic coma; liver transplantation was required. Glimepirid and estradiol were used as co-medication. A causal connection between the liver effect and kava intake cannot definitely be excluded. However, contribution by the co-medication to the side effect seems possible.

A further case report on kava (Strahl et al., 1998) describes a necrotising hepatitis in a 39-year old female patient with positive re-exposition. During the first application of the kava product, an oral contraceptive as well as paroxetin were used. A causal relationship with kava cannot be excluded, but the patient's history and a potential pre-existing liver damage must be taken into account. In addition, the kava preparation used was not identified by the physician.

In additional reports from Switzerland, Escher et al. (2001) and Stoller, (2000) describe two cases: a liver transplantation in a 50-year old female patient using also evening primrose oil, a yeast preparation and paracetamol as well as liver symptoms in a 33-year old patient who also applied propyphenazon and paracetamol and consumed alcohol.

Most of the other case reports (not quoted by BfArM) cannot be assessed since essential data are missing, or they have to be evaluated as “improbable” or “questionable.”

Data on the Benefit Assessment

According to a meta-analysis performed by Pittler and Ernst (2001), therapeutic equivalence of kava and synthetic anxiolytics can be assumed.

For an extract prepared with acetone as [a] solvent, there are seven randomised placebo-controlled double blind studies as well as one randomised reference-controlled double blind study performed between 1991 and 2001. They demonstrate the efficacy of the kava extract in conditions of nervous anxiety, stress and restlessness.

On various ethanolic extracts, the following data are available:

- A three-arm double-blind clinical study in 127 patients versus opipramol and buspirone in order to prove efficacy in general conditions of nervous anxiety
- A non-interventional study in 1187 patients confirming these results and demonstrating good tolerability
- A pharmacodynamic study versus bromazepam and placebo showing relaxing and anxiolytic effects of a kava extract as well as better tolerability than bromazepam
- An *in-vivo* experiment (elevated plus maze test in rats) showing a remarkable anxiolytic effect of a kava extract comparable to that of diazepam
- A randomised, controlled, double-blind study in 69 patients demonstrating improvement of the total Hamilton Anxiety Scale score as well as for the score for [psychologic] and somatic anxiety at a dose of 200 mg kavapyrones daily
- A study demonstrating a tranquillising effect (comparable to benzodiazepines) in conditions of anxiety prior to medical surgery
- A non-interventional study in 3338 patients demonstrating a remarkable decrease in symptoms of anxiety after an average duration of therapy of 2.5 months
- An observational study in 52 patients showing a decrease of anxiety-related symptoms
- An observational study including 30 patients with psycho-somatic complaints which demonstrated improvement
- Further experiments with a lower number of patients as well as a non-interventional study currently being performed including 131 patients.

As a result of their proven clinical efficacy, kava preparations were included in the draft positive list issued by the German ministry of health in July 2001. According to this draft list, kava products are reimbursable by the state health insurance like chemical substances used in this indication field.*

Conclusion

Conditions of nervous anxiety, stress and restlessness must be regarded as wide-spread disorders which, without treatment, might have severe [psychologic] and social consequences and for this reason require medical treatment. In case kava products are withdrawn from the market, only chemical substances would be available as therapeutic alternatives, e.g. benzodiazepines, anxiolytics, anti-depressants, neuroleptics, et cetera. Yet, all these substances have

*Note added: An indication field is a range of indications, for example, anxiety, for reimbursement under the state medical system in Germany.

many side-effects, including liver toxicity. Benzodiazepines as an alternative have a high potential of addiction.

Available data on the benefit–risk assessment of kava and kava-containing medicinal products do not justify the withdrawal of the respective marketing authorisations. Inform[ing] . . . the patient by package leaflets as well as expert information and [supervision] of patients by a physician are regarded as an appropriate means [using kava].

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